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Research trends on the use of ultrasound as neuromodulation-based therapy, based on bibliometric analysis

Arman Yurisaldi Saleh[1*], Tony Setiobudi[2], Muhammad Shiddiq Sayyid Hashuro[3]

[1]Neurology Department Faculty of Medicine UPN Veteran Jakarta, Indonesia;
[2]Orthopaedic Departemen,ount Elizabeth Hospital, Singapore;
[3]Biomedical Engineering Department, School of Electrical Engineering and Informatics, Bandung Institute of Technology, Indonesia.

*Corresponding author:
Arman Yurisaldi Saleh;
Neurology Department Faculty of Medicine UPN Veteran Jakarta, Indonesia;
drarmanyurisaldic@gmail.com

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ABSTRACT

Introduction: Ultrasound has seen a significant increase in use in neuromodulation-based therapy over the past decade due to technological advancements, enabling precise tissue ablation, clinical neuromodulatory brain stimulation, and targeted blood-brain barrier permeabilization. The bibliometric analysis reveals a growing body of literature focused on the utilization of low-intensity ultrasound (LI-US) and high-intensity focused ultrasound (HIFUS) in the field of neuromodulation. Ultrasonography has potential applications in treating neurological and psychiatric illnesses like neuropathic pain, epilepsy, and treatment-resistant mental illness, but further investigation is needed to understand mechanisms and safety considerations. The use of bibliometric analysis can effectively identify common research patterns and highlight advancements in this specific academic field. Research indicates that ultrasound-based neuromodulation approaches may offer novel therapeutic interventions with enhanced efficacy and safety in treating various neurological and mental illnesses.
Methods: The process of data collection involved conducting a search on the Scopus website using specific keywords. Subsequently, the collected data is stored in the file formats of .bib and .csv. These files are then subjected to analysis using the biblioshiny and Vosviewer software tools. The research not only use quantitative analysis but also incorporates qualitative investigations.
Results: The trend of the most significant affiliations, authors, documents with the highest number of citations, relevant sources, cited nations, and annual scientific production was determined. This academic study employs many visualization techniques, including overlay visualization of the Scopus database, utilization of VOSviewer for database analysis, network visualization, density visualization, and thematic mapping.
Conclusions: The use of ultrasound as a neuromodulation therapy offers numerous opportunities and potential across various sub-topics, despite a limited literature corpus compared to other academic disciplines. The use of this discipline in human subjects is limited, requiring extensive clinical studies and cross-national collaboration for the advancement of therapeutic interventions.

Keywords: Trend research, ultrasound, neuromodulation, therapy, applied, bibliometric.
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INTRODUCTION

Neuromodulation is a methodology employed to modulate the functioning of the nervous system through the application of stimuli that either enhance or suppress nerve impulses. In recent years, there has been a growing trend in the utilization of ultrasound as a prominent method for neuromodulation-based therapy.[1] Recent technological advancements have enabled ultrasound to effectively penetrate the human skull, facilitating precise tissue ablation, clinical neuromodulatory brain stimulation, and targeted disruption of the blood-brain barrier. The bibliometric analysis reveals a growing body of literature focused on the utilization of low-intensity (LI-US) and high-intensity (HIFUS) ultrasound for the purpose of neuromodulation.[2] Multiple studies have indicated the potential application of ultrasound as a therapeutic modality for neurological and psychiatric conditions, including neuropathic pain, epilepsy, and treatment-resistant mental disorders.[3] Further investigation is necessary in order to comprehensively comprehend the mechanisms and safety considerations associated with the utilization of ultrasound in the field of neuromodulation. Within this particular context, the utilization of bibliometric analysis might serve as a valuable tool for discerning research trends and elucidating advancements within the topic at hand.[2,4] There is an optimistic outlook that additional research endeavors will provide novel, enhanced, and secure therapeutic interventions for diverse neurological and mental illnesses through the utilization of neuromodulation approaches based on ultrasound

METHODS

This study employs quantitative analytic techniques utilizing bibliometrics, specifically employing the Biblioshiny and VOSviewer apps. The data is sourced from Scopus due to its comprehensive nature and current status as a leading data repository known for its high data quality.

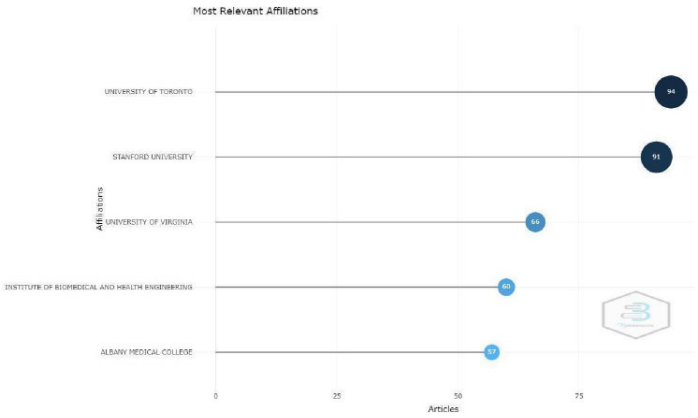

Figure 1. Most relevant affiliations.

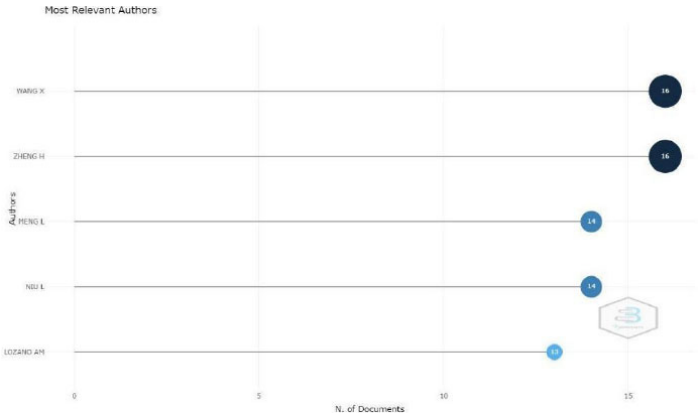

Figure 2. Most relevant authors.

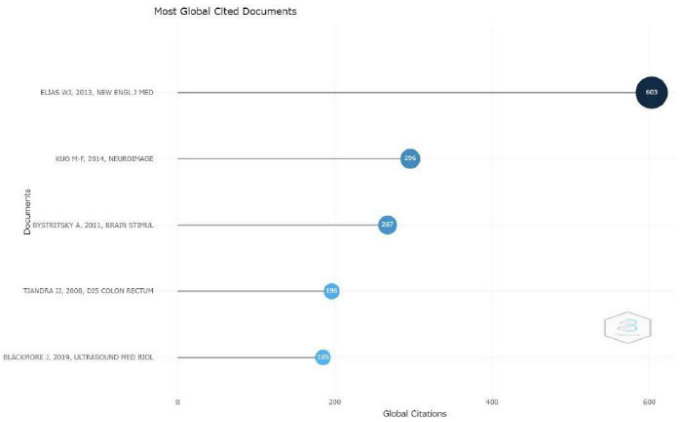

Figure 3. Most global cited documents.

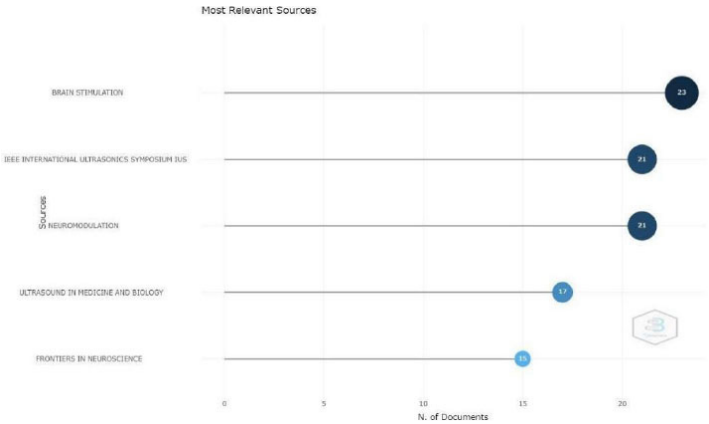

Figure 4. Most relevant sources.

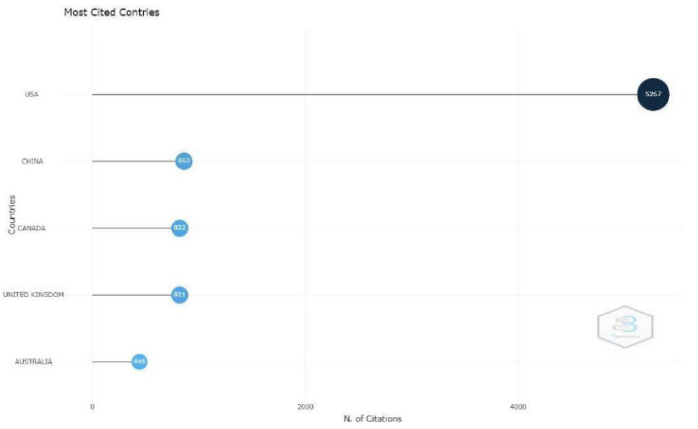

Figure 5. Most cited countries.

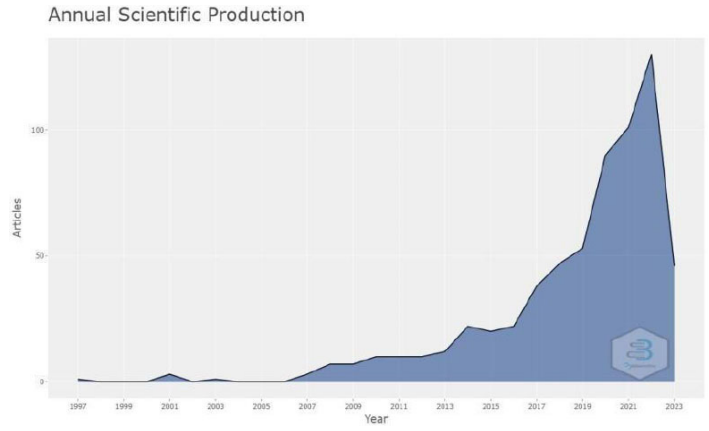

Figure 6. Annual scientific production

The utilized terms encompass vagus stimulation, vagal stimulation, auricular, and human.

Data Collection

A search was conducted on the Scopus database, which is known for its collection of reputable research articles. The search was performed using certain keywords, including "ultrasound" in the title, abstract, and keywords, as well as "neuromodulation" in the same fields. Additionally, the keywords "therapy" or "treatment" were included in conjunction with the keyword "bibliometric" in the title, abstract, and keywords. A total of 633 documents were obtained. Subsequently, the document obtained from Scopus is preserved by means of saving it in the file format denoted by the extension ".The dataset encompasses the years 1997 to 2023. The study was carried out between the dates of August 17, 2023, and August 27, 2023.

Data Analysis

The analysis was conducted with bibliometric analysis and Vosviewer software.

RESULTS

The obtained findings of our quantitative analysis revealed a discernible inclination

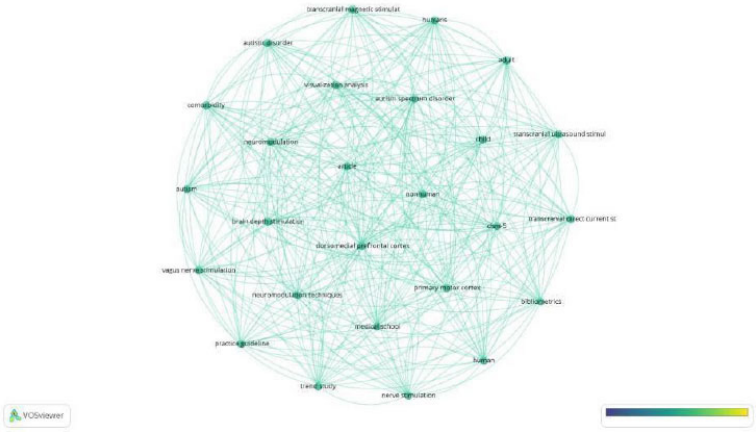

Figure 7. Overlay visualization of scopus, database using vosviewer.

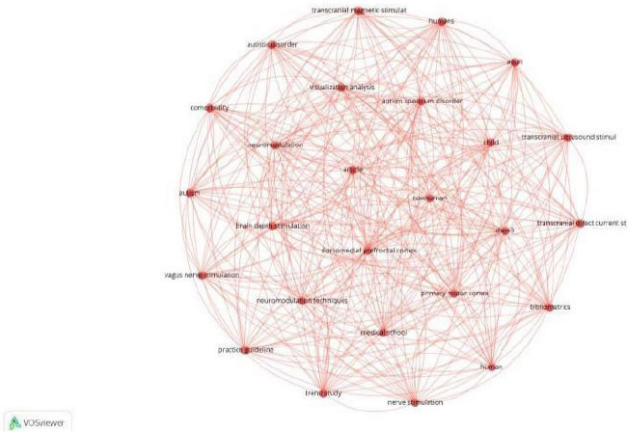

Figure 8. Network visualization.

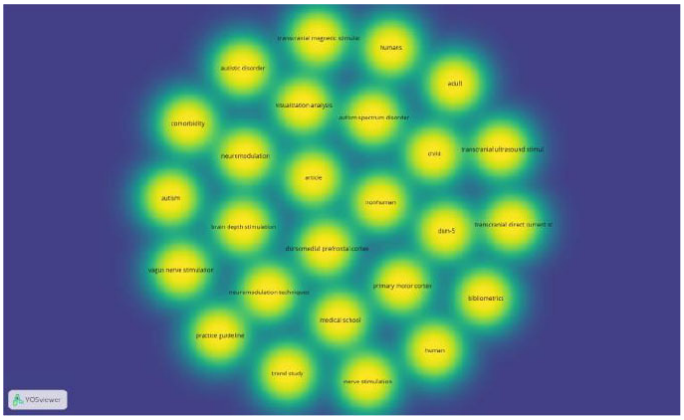

Figure 9. Density visualization.

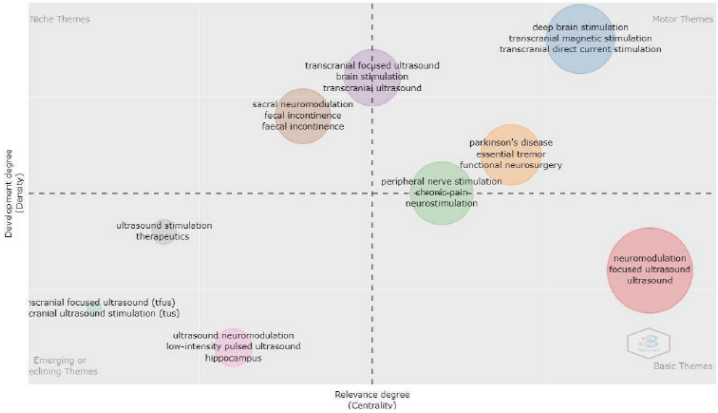

Figure 10. Thematic map.

towards a rise in the production of documents pertaining to this particular field. These documents encompassed a wide range of situations, were authored by individuals who contributed the most to this body of literature, originated from countries that exhibited the highest document output, and covered both saturated and unsaturated research areas. Furthermore, our analysis identified emerging themes within this field, as well as instances of research collaboration between countries. Additionally, a qualitative analysis was conducted in parallel.

Quantitative Analysis

Most Relevant Affiliations

According to the data presented in Figure 1, the University of Toronto in Canada exhibits the greatest count of Scopus indexed documents among the affiliates. The University of Toronto is home to prominent researchers who specialize in the application of ultrasound for neuromodulation. Dr. Nir Lipsman, an esteemed academic, holds the position of Associate Professor within the Department of Surgery at the University of Toronto. Additionally, he serves as a distinguished scientist affiliated with the Sunnybrook Research Institute, further solidifying his significance within this particular sector. In addition to his role as Director of the Harquail Center for Neuromodulation at Sunnybrook, Dr. Lipsman also holds the position of Director. Dr. Lipsman has acquired expertise in various disciplines, such as neuromodulation, magnetic resonance-guided focused ultrasound, and deep brain stimulation. The email address of Dr. Lipsman can be reached at nir.lipsman@sunnybrook.ca. In addition to Dr. Lipsman, Anton Fomenko is also actively engaged in doing research pertaining to the application of ultrasound in neuromodulation. Anton Fomenko is currently associated with the Institute of Medical Sciences at the University of Toronto. Nevertheless, more information. In relation to areas of specialization and proficiency, The sources mentioned do not contain Anton Fomenko's email address.[5]

Stanford University is actively engaged in the domain of neuromodulation utilizing ultrasound, with a number of researchers dedicated to this area of investigation. Dr. Kim Butts Pauly, a professor in the Department of Radiology at Stanford University and the head of the Kim Butts Pauly Lab, is recognized as a prominent researcher in this particular subject. Dr. Pauly has expertise in various domains, including the application of focused ultrasound therapy, utilization of imaging technology, and the treatment of neurological disorders and cancer. Unfortunately, the source provided does not include any information regarding the availability of Dr. Pauly. In addition to Dr. Pauly, Raymond McKoy is also engaged in research pertaining to the application of ultrasound in neuromodulation. Raymond McKoy is associated with The Maduke Lab, a research group located

Table 1. The result of cluster analysis

Hal	Cluster	Most Frequent Word	Keyword
1	Cluster 1		adult (25) article (25) autism (25) autism spectrum disorder (25) autistic disorder (25) bibliometric (25) brain depth stimulation (25) child (25) comorbidity (25) dorsomedial prefrontal cortex (25) dsm-5 (25) human (25) humans (25) medical school (25) nerve stimulation (25) neuromodulation (25) neuromodulation techniques (25) nonhuman (25) practice guidline (25) primary motor cortex (25) transcranial direct current stimulation (25) transcranial magnetic stimulation (25) trend study (25) vagus nerve stimulation (25) visualization analysis (25)

Table 2. Summarized documents related to therapy in the field of ultrasound as neuromodulation

No.	Theme	Number of Documents
1	Pain	74 Document [6-77]
2	Neuroinflammation	1 Document [78]
3	Neuropsychiatric illness	165 Document [79-243]
4	Immunomodulation	1 Document [244]
5	Atrial fibrillation	1 Document [245]
6	Non-invasive visual prostheses	1 Document [246]
7	Ultrasound Surgery	1 Document [247]
8	Endometriosis	1 Document [248]
9	Treatment of atrioventricular block	1 Document [249]
10	Hypertension	4 Document [250-253]
11	Myocardial ischemia–reperfusion injury	2 Document [254, 255]
12	Modulates the effects of drugs	3 Document [256-258]
13	Editorial comment	1 Document [259]
14	Discussion (Book Chapter)	1 Document [260]
15	Hyperhidrosis	1 Document [261]
16	Functional anorectal disturbances	1 Document [262]
17	Myopia	1 Document [263]
18	Neuro-urology	52 Document [264-315]
19	Neurosurgery	7 Document [5, 316-321]
20	The research group is not yet applicable	315 Document [1, 3, 4, 322-632]

at Stanford University. The individual has a keen interest in the phenomena of neuromodulation through the utilization of ultrasound. Presently, their primary focus lies in the optimization of parameters and mechanisms associated with the neuromodulatory effect. The email address associated with Raymond McKoy is rmckoy@stanford.edu.

The University of Virginia is actively engaged in the field of neuromodulation utilizing ultrasound, with multiple researchers contributing to this area of study. Dr. Wynn Legon, an esteemed researcher, holds a position within the Department of Neurology at the University of Virginia. His scholarly pursuits mostly revolve around the exploration of transcranial focused ultrasound (tFUS) and its associated research endeavors. In addition to Dr. Legon, Dr. Jeffrey Elias is a notable person in this domain, recognized for his contributions in advancing targeted ultrasound technology for the non-invasive treatment of many neurological illnesses. However, the availability of Dr. Legon and Dr. Elias cannot be confirmed based on the provided source.

Most Relevant Authors

According to Figure 2, the individuals who have the highest numerical values are Wang Xingran, Zheng Hairong, and Meng Long. Wang Xingran is currently associated with Yanshan University, located in Qinhuangdao, China. Zheng Hairong is associated with the University of Chinese Academy of Sciences, located in Beijing, China. Meng Long is associated with the Shenzhen Institute of Advanced Technology, located in Shenzhen, China.

Most Global Cited Documents

According to Figure 3, The article titled "A Pilot Study of Focused Ultrasound Thalamotomy for Essential Tremor" was authored by Elias WJ and was published in 2013 in the New England Journal of Medicine. This article presents a study that examines the initial findings of a research endeavor centered on ameliorating essential tremor in a cohort of 15 individuals through the utilization of MRI-guided focused ultrasound thalamotomy. This article contains the highest number of instances, specifically 603 citations.

The publication titled "Real-time 3D ultrasound imaging of infant tongue movements during breast-feeding," authored by Kuo MF and published in 2014 in the journal NeuroImage, holds the second position in terms of citation count with a total of 296 citations. The present paper examines the application of real-time three-dimensional (3D) ultrasound imaging technology for the

purpose of observing the dynamic motion of an infant's tongue during the process of eating.

The paper titled "A review of low-intensity focused ultrasound pulsation" authored by Bystritsky A and published in 2011 in the journal Brain Stimulation holds the third position with a total of 267 citations. This article provides an overview of the historical context, underlying justification, and preliminary investigations pertaining to a novel technique of brain stimulation known as low intensity focused pulsed ultrasound (LIFUP).

Most Relevant Sources

According to Figure 4, the journal that has the top ranking in terms of relevance is Brain Stimulation. The journal "Brain Stimulation" is indexed in Scopus and is published by Elsevier. The inception of this scholarly publication occurred in the year 2008, with a primary emphasis on the domain of neuromodulation. The magazine encompasses a range of neuromodulation technologies, including transcranial magnetic stimulation, deep electrical brain stimulation, transcranial direct current stimulation, ultrasonic neuromodulation, and optogenetics. According to the Scimago Journal Rank (SJR), the Journal Brain Stimulation achieved an SJR score of 3,042 in the year 2021. The aforementioned journal has been classified inside the Q1 category for the academic disciplines of Biophysics and Neurology (clinical). The individual holding the position of editor-in-chief for the Journal Brain Stimulation is Mark S. George, MD, who is professionally associated with the Medical University of South Carolina, located in Charleston, South Carolina, United States. In relation to the duration of article review for submissions made to this journal, the average period from submission to manuscript receipt, as reported by the Brain Stimulation Review Speed Feedback System, is 10.0 days.

The IEEE international ULTRASONICS SYMPOSIUM IUS is considered the second most significant source. The IEEE International Ultrasonics Symposium (IUS) is a conference that is indexed in Scopus. It is conducted by IEEE, which is recognized as the largest non-profit organization globally, with a primary objective of improving technology for the betterment of humanity. The International Ultrasonics Symposium (IUS) is a renowned conference that serves as a platform for scholarly discussions on a wide range of issues within the ultrasonic field. These themes encompass diverse areas such as medical applications, sensor technology, non-destructive evaluation (NDE) techniques, industrial applications, physical acoustics, and microacoustics. According to the Scimago Journal Rank (SJR), the International University of Science (IUS) achieved an SJR score of 0.265 in the year 2020. The IUS conferences are annually conducted at diverse venues. In the year 2022, the aforementioned conference is scheduled to take place in the city of Venice, located in Italy.

The magazine "Neuromodulation" holds the third position in terms of relevance within the ranking of sources. The Journal of Neuromodulation: Technology at the Neural Interface is a scholarly publication that is indexed in Scopus.

The publication will be initiated by Elsevier commencing in January 2022. This magazine serves as the designated publication of the International Neuromodulation Society (INS) and is dedicated to the scholarly exploration of the topic of neuromodulation. The magazine encompasses a wide range of topics pertaining to neuromodulation, including advancements in neural interface technology, clinical applications, translational studies, and fundamental scientific research. According to the Scimago Journal Rank (SJR) metric, the journal Neuromodulation achieved an SJR score of 0.827 in the year 2023. The magazine in question has been classified under the Q2 category for the disciplines of Anesthesiology and Pain Medicine, Medicine (miscellaneous), Neurology, and Neurology (clinical). The individual holding the position of Editor-in-Chief for the journal is Robert M. Levy, MD, PhD. The headquarters of the editorial office for this publication is located in San Francisco, California, within the United States of America.

Most Cited Countries

Figure 5 illustrates that the United States, China, and Canada are the leading countries in terms of receiving the highest number of publication citations worldwide pertaining to the utilization of ultrasound for neuromodulation. This prominence can be attributed to various factors. Firstly, it is important to note that these countries possess robust research infrastructure and substantial financial backing for research endeavors within this field. Furthermore, several prominent research institutions specializing in ultrasound-based neuromodulation are situated in the aforementioned nations, including Stanford University, University of Southern California, and Washington University in the United States. Furthermore, scholarly investigations conducted within these nations frequently find their way into prestigious journals characterized by high impact factors and wide readership, hence augmenting the probability of receiving citations. Furthermore, it is noteworthy that these nations exhibit robust worldwide partnerships in the field of neuromodulation research, hence augmenting the prominence and acknowledgement of their respective research endeavors. Furthermore, the research trends seen in these countries encompass the advancement of novel and cutting-edge technology in the field of ultrasound-based methodologies.

Neuromodulation techniques, such as the utilization of capacitive micromechanical ultrasonic transducers (CMUT) and piezoelectric (PUT), have been employed to enhance the accuracy and efficacy of stimulation. The scope of this study encompasses a diverse array of clinical applications, including the management of neuropathic pain, epilepsy, and treatment-resistant psychiatric conditions.

Annual Scientific Production

According to the data presented in Figure 6, there is a discernible pattern of growth in the quantity of scholarly publications pertaining to the subject of ultrasound for neuromodulation throughout the period spanning from 1997 to 2023.

Overlay Visualization of Scopus, Database Using Vosviewer

In figure 7, in the overlay visualization picture, the same color appears on all existing topics. This shows that all topics become research trends.

Network visualization

The diagram presented in Figure 8 illustrates network visualization. The Network visualization of diverse research topics within the domain of utilizing ultrasound for neuromodulation reveals a limited quantity of studies, indicating a significant research gap that remains open for further exploration and advancement. This encompasses various research areas, including those associated with bibliometrics.

According to the findings derived from the network visualization study conducted using the Vosviewer program, it is evident that the interconnections among research topics exhibit a somewhat balanced distribution across various subjects. Both tissues exhibit similar density levels. This observation suggests that there remains untapped study potential in exploring the interconnections between various areas.

Density visualization

The diagram presented in Figure 9 density visualization. The density visualization overview generated by the Vosviewer software study indicates that there is no discernible variation in density among the themes. The distribution of themes is very even, allowing for the possible development of research across several areas. There is no subject matter that has reached a point of research saturation.

Thematic map

Figure 10 illustrates the emerging research trends within the Niche Theme sector, namely transcranial focused ultrasound, brain stimulation, transcranial ultrasound, and sacral neuromodulation.

The Motor Theme section exhibits a substantial body of research encompassing various topics, including deep brain stimulation, transcranial magnetic stimulation, transcranial direct current stimulation, Parkinson's disease, essential Tremor, functional neurosurgery, peripheral nerve stimulation, and chronic pain neurostimulation.

Within the main topic segment, various fields have been identified in study, specifically neuromodulation, focused ultrasound, and ultrasound. The rising and declining themes area includes topics such as ultrasonic neuromodulation, low intensity pulse ultrasound, the hippocampus, ultrasound stimulation treatments, transcranial focused ultrasound, and transcranial ultrasound stimulation.

Cluster Analysis

From Table 1, there is only one cluster in the document review results using the Vosviewer application with the same power. This shows that there is no dominance of research topics and all topics have the potential to be explored more.

Qualitative Analysis

In Table 2, qualitatively, it appears based on qualitative analysis that the applicable use of ultrasound for neuromodulation therapy in humans is dominated by neuropsychiatry, pain and neuro-urology cases. Meanwhile, other fields of science have barely been used in an applied way. Based on this, clinical trials must be increased so that a greater number of applications in this field can be called therapy for humans in various fields of health science more broadly.

DISCUSSION

Ultrasound has become a topic of interest in neuromodulation research due to its ability to non-invasively stimulate the brain with better spatial precision and target deeper depths.[633] Several studies have demonstrated the positive effects of using low-intensity ultrasound (LI-US) in neuromodulation, fracture healing, inflammation repair, and metabolic regulation. More recent research has demonstrated the potential use of focused ultrasound (fUS) in the treatment of epilepsy and sleep disorders and psychiatric disorders.[633-635] Mechanisms and Safety The mechanisms underlying ultrasound neuromodulation involve interactions between ultrasound waves and brain tissue, which can produce excitatory or inhibitory effects on neuronal activity. In general, the literature supports the use of ultrasound as a safe and non-invasive brain stimulation modality.

Based on literature studies, no serious complications were found when using ultrasound in neuromodulation therapy.[199,209,395]

A bibliometric study covering the period 1995-2022 found 7209 LI-US related articles. This study highlights the increased interest in ultrasound-based neuromodulation research in recent decades. From this analysis, research trends in the use of ultrasound as a neuromodulation-based therapy show increasing interest and potential for broad clinical applications. However, more research is needed to fully understand the mechanisms underlying the neuromodulatory effects of ultrasound and to optimize the stimulation parameters to be safe and effective in various clinical conditions.

The bibliometric research that we conducted retrieved data from the Scopus database, which is different from researchers who have published bibliometric research on similar topics from the Web of science database, with the consideration that the Scopus database has a wider scope than the Web of Science.

The weakness of this study is that if other researchers use different keywords, different results will also be obtained.

CONCLUSIONS

With this research, research gaps can be identified and it is necessary to form new networks in terms of research between countries so that applications in the clinical use of ultrasound neuromodulation can be accelerated and reproduced. Research progress in this field related to therapy of diseases in neurology is largely determined by the politics of a country in supporting funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

FUNDING

This research received no external funding.

AUTHOR CONTRIBUTION

AYS collects data, processed and analyzes, prepare manuscript, TS and MSSH edits manuscript.

ETHICAL STATEMENT

This study used secondary data retrieved from database that do not require approval from the Ethics Committee for research on humans. However, we followed the ethical principles recommended for analysis of this nature through respecting ideas and citations and referencing authors and their publications

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